

Prospective, Randomized Trial of Prolonged Intracoronary Urokinase Infusion for Chronic Total Occlusions in Native Coronary Arteries

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Objectives. The purpose of this study was to determine the safety and efficacy of three dosing regimens of intracoronary urokinase for facilitated angioplasty of chronic total native coronary artery occlusions.

Background. Percutaneous transluminal coronary angioplasty of chronically occluded (>3 months) native coronary arteries is associated with low initial success secondary to an inability to pass the guide wire beyond the occlusion.

Methods. Patients were enrolled if a chronic total occlusion >3 months old could not be crossed with standard angioplasty equipment. Of the 101 patients enrolled, 41 had successful guide wire passage and were excluded from urokinase treatment. The remaining 60 patients were randomized to receive one of three intracoronary dosing regimens of urokinase over 8 h (group A = 0.8 million U; group B = 1.6 million U; group C = 3.2 million U), and angioplasty was again attempted after completion of the urokinase infusion in 58 patients.

Results. Coronary angioplasty was successful in 32 patients

(53%) (group A 52%, group B 50%, group C 59%, $p = 0.86$). This study had a 90% power to detect at least a 50% difference between dosing groups at alpha 0.05. Bleeding complications requiring blood transfusion did not differ significantly among the dosing groups (A 0%, B 15%, C 6%, $p = 0.14$), although major bleeding episodes were less common in group A ($p < 0.05$). There were no major procedural or in-hospital complications. Angiographic follow-up in 69% of the patients with successful angioplasty revealed target vessel patency in 91% but an angiographic restenosis rate of 59%.

Conclusions. A prolonged supraselective intracoronary infusion of urokinase can be safely administered and may facilitate angioplasty of chronic total occlusions. Lower doses of urokinase are equally effective and result in fewer bleeding complications than do higher dosage regimens. Vessel patency is frequently maintained, but restenosis remains a problem.

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Conventional percutaneous transluminal coronary angioplasty of chronically occluded native coronary arteries has been associated with lower initial success rates as well as higher restenosis rates than those associated with elective angioplasty of nonoccluded vessels (1). Reported initial success of angioplasty of chronic total occlusion rates range from 47% to 67% (mean \pm SD $61 \pm 7\%$) (1-7). However, the study patients were highly selected and many of these series included patients with subacute (<1 month) or functional (99% stenosis) occlusions, which are associated with better primary success rates. Even after successful balloon angioplasty, 6-month angiographic restenosis rates range from 41% to 71% (mean $54 \pm 11\%$) and reocclusion rates range from 20% to 40% (5-9).

The most frequent cause for failure of angioplasty in chronic total occlusions is the inability to cross the occlusion with a guide wire, particularly in occlusions of >3 months' duration (10,11). Reported success rates in this subgroup are consistently lower than those associated with more recent total occlusions and have ranged between 0% to 55% (12,13). Because of the low probability of success, chronic total occlusions of >3 months' duration are usually not considered for percutaneous intervention, and are often referred for bypass surgery. However, successful recanalization of chronic total occlusions has been shown to reduce anginal symptoms, decrease the need for coronary artery bypass surgery and improve left ventricular function (5,14). Thus, new techniques to recanalize chronic total occlusions are of great interest to interventional cardiologists.

Prolonged infusion of thrombolytic agents has resulted in recanalization of chronically occluded saphenous vein grafts and peripheral arteries (15,16). A pilot study of intracoronary urokinase infusion in native coronary occlusions demonstrated that a prolonged (8- to 24-h) infusion could be safely performed and appeared to facilitate passage of the guide wire

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(17). The present larger prospective, randomized trial was performed to determine the safety and efficacy of three dosing regimens of intracoronary urokinase for chronic total native coronary artery occlusions when guide wire passage beyond the lesion could not be achieved.

Methods

Study patients. The study group was composed of 101 patients undergoing elective coronary angioplasty of a chronic occlusion in a native coronary artery. These patients had Canadian Cardiovascular Society class II to IV angina or a reversible myocardial perfusion defect in the distribution of a coronary occlusion, or both. Inclusion criteria included a chronic occlusion of >3 months' duration as assessed by previous cardiac catheterization, change in anginal symptoms or a prior failed angioplasty attempt. To ensure adequate delivery of urokinase to the point of occlusion, patients with a large side branch or with extensive bridging collateral vessels at the point of occlusion were excluded. Additional exclusion criteria included contraindication to thrombolytic therapy (history of cerebrovascular accident, known bleeding disorder, severe uncontrolled hypertension, major surgery or trauma within 60 days), chronic atrial fibrillation with underlying mitral valve disorder, and inability to advance the infusion catheter to the proximal portion of the occlusion. The study protocol was approved by the Institutional Review Board of William Beaumont Hospital and written informed consent was obtained from each patient before recruitment.

Urokinase protocol. Patients were pretreated with 325 mg of chewable aspirin and received a bolus of 10,000 U of intravenous heparin, with additional boluses given to maintain an activated clotting time >300 s. Patients scheduled for a urokinase infusion were brought to the catheterization laboratory in the morning and an attempt was made to cross the occlusion with a guide wire. A 7F guiding catheter was inserted through the femoral artery and seated in the ostium of the occluded coronary artery. A Touhy-Borst adapter (ACS) was attached to the end of the guiding catheter and a 0.038-in. (0.096-cm) Cragg infusion wire (Meditech) was advanced over a 0.018-in. (0.046-cm) guide wire. Guide wires of increasing stiffness (Intermediate and Standard wires) were employed and an 0.018-in. standard wire was attempted before instituting the urokinase infusion in all cases. The 41 patients whose lesions were successfully crossed were excluded, whereas the remaining 60 patients whose occlusion could not be crossed were randomized to one of three urokinase dosing regimens. Contrast medium was injected through the Cragg wire to ensure that it was embedded in or just proximal to the occlusion. Intracoronary urokinase (Abbokinase, Abbott Laboratories) was then infused for approximately 8 h through the guiding catheter proximally and the Cragg infusion wire distally. With the use of sealed randomization envelopes, patients were randomized in unblinded fashion to three different dosing regimens of urokinase. Urokinase doses were derived from previous studies using urokinase infusions in occluded sapherous vein grafts.

The duration of infusion was limited to 8 h to reduce the bleeding complications of a 24-h infusion and to maintain catheterization laboratory convenience. Group A received 50,000 U/h of urokinase through the guide catheter and 50,000 U/h through the Cragg infusion wire for a total of 800,000 U over 8 h. Group B received 100,000 U/h through each port for a total of 1.6 million U over 8 h. Group C received 200,000 U/h through both the guide and the infusion wire for a total of 3.2 million U over 8 h. The catheter and the femoral sheath were sutured to the skin to ensure stability and were covered with a sterile dressing.

Patients were then monitored in the cardiac care unit while intravenous heparin and intracoronary urokinase infusions were continued. A broad spectrum intravenous antibiotic agent was administered during the urokinase infusion. The patient's hemoglobin, fibrinogen, fibrin split products, creatinine kinase, activated clotting time and partial thromboplastin time were monitored. Activated clotting time was maintained between 200 and 250 s while the patient was in the cardiac care unit. After ~8 h, the patient returned to the catheterization laboratory for a second attempt to cross the occlusion. A similar approach, using wires of increasing stiffness, was again employed. If the lesion was successfully crossed, balloon angioplasty was performed. No other interventional devices were used during the primary procedure. Procedural success was defined as successful guide wire passage and a final residual diameter stenosis <50% with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow. Clinical success was defined as procedural success without a major in-hospital cardiac event.

Follow-up. If the procedure was successful, administration of warfarin was initiated and continued for 3 to 4 months (prothrombin time was maintained between 18 and 22 s, international normalized ratio 2.0 to 3.0), treatment with aspirin was continued and additional medical therapy was administered at the discretion of the cardiologist. Patients with successful coronary angioplasty after the urokinase infusion were followed up clinically and were requested to undergo an elective stress thallium test at 3 months and a follow-up catheterization at 6 months. Clinical restenosis was defined as death or the need for target vessel revascularization during the 6-month follow-up period divided by the total number of successful angioplasties. Angiographic restenosis was defined as >50% diameter stenosis by quantitative angiography in the target lesion at follow-up.

Statistical analysis. Immediate procedural results and complications were compared among the urokinase dosing groups. All data are displayed as a mean value \pm SD. Significance testing was performed by using analysis of variance (ANOVA) testing where appropriate. Statistical significance was accepted at the $p < 0.05$ level.

Results

Baseline characteristics. The flow diagram in Figure 1 summarizes the number of patients at each stage of the

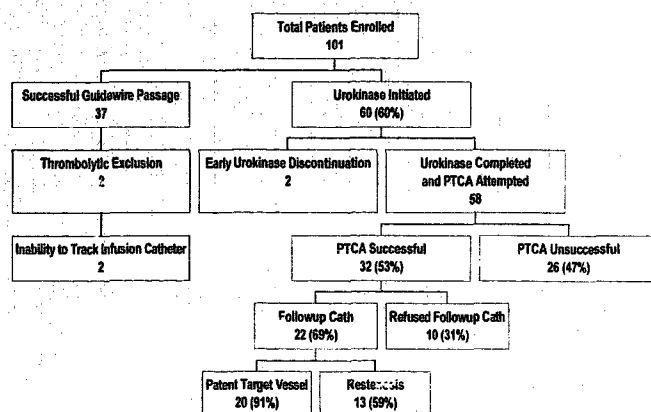


Figure 1. Flow diagram demonstrating the number of patients at each stage of the protocol. Cath = cardiac catheterization; PTCA = percutaneous transluminal coronary angioplasty.

protocol. Although 101 patients gave consent to enter the study, 41 patients did not receive urokinase and were excluded secondary to successful crossing of the occlusion with the guide wire on the initial attempt ($n = 37$), contraindications to thrombolytic therapy ($n = 2$) or inability to track the infusion catheter into the occlusion ($n = 2$). Sixty patients had unsuccessful angioplasty and were then randomized to receive urokinase infusions. Two patients, both randomized to group C, required early discontinuation of the urokinase infusion. One patient experienced a transient ischemic attack during placement of the infusion catheter, although this was not recognized until the urokinase infusion was initiated. The other patient experienced gastrointestinal bleeding after 30 min of urokinase infusion, attributed to a Mallory-Weiss tear secondary to vomiting that began after the left ventriculogram was performed. Baseline patient demographics for the 60 patients randomized are shown in Table 1.

The mean age of the patients was 56 ± 10 years and the mean duration of occlusion was 23 ± 16 months. The chronic occlusion was located in the left anterior descending coronary artery in 27%, the left circumflex coronary artery in 13% and the right coronary artery in 60%. The majority of patients had

multiple cardiac risk factors and 33% had prior revascularization. Fifty-two percent of patients had a prior documented myocardial infarction in the distribution of the occluded target vessel. Eighty-seven percent had at least class II anginal symptoms at the time of the procedure, whereas 13% had angina-equivalent symptoms (shortness of breath, fatigue) and positive findings on a functional test.

Procedural results. All patients had TIMI grade 0 flow at the start of the procedure. Fifty-eight patients (97%) completed the urokinase infusion and returned for repeat angiography and attempted coronary angioplasty. The urokinase infusion improved flow from TIMI grade 0 to TIMI grade 1 in only 5 patients (9%). Despite the lack of angiographic improvement with urokinase, the guide wire was successfully passed in 34 cases (59%); however, two patients were not considered to have had successful angioplasty because of a residual 50% to 70% stenosis and TIMI grade 2 flow. Therefore, angioplasty was successful in 32 patients (53%) after the urokinase infusion (Fig. 2). Balloon angioplasty success rates for groups A, B and C were 52%, 50% and 59%, respectively ($p = 0.86$, chi-square = 0.31, $df = 2$) (Table 2). A power analysis assuming $\alpha = 0.05$ revealed that the study had a 90% power to detect a $\geq 50\%$ difference between the groups. Differences between angioplasty success rates for the three major coronary vessels were also not statistically significant ($p = 0.9$).

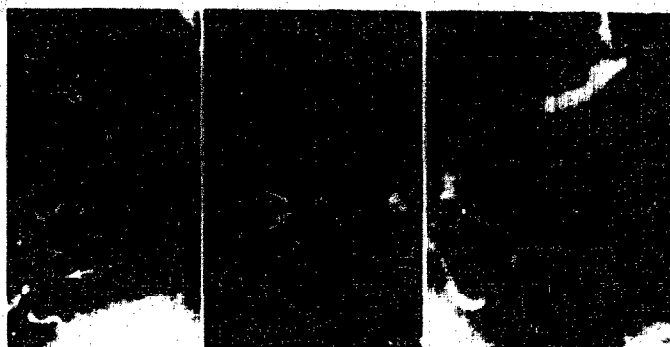
Complications. There were no major procedural complications including stroke, need for emergency bypass surgery or death, yielding a clinical success rate of 53%. Chest pain occurred in 20% of patients during the urokinase infusion; however, only one of these patients had ischemic electrocardiographic changes. Two patients (3%) had an embolic event manifested by transient visual disturbances—one patient before and one after the urokinase infusion was initiated. Non-flow-limiting dissections in 30% of patients were the only

Table 1. Baseline Characteristics of the 60 Randomized Patients

Age (yr)	56 ± 10
Male	78%
Smoking history	64%
Hypertension	66%
Diabetes	20%
Cholesterol >240	53%
Previous angina	86%
Previous CABG	7%
Previous MI in distribution of occluded target vessel	52%
Duration of occlusion (mo)	23 ± 16

Data are presented as mean \pm SD or percent of patient group. CABG = coronary artery bypass graft surgery; MI = myocardial infarction.

Figure 2. Selective angiograms of the right coronary artery demonstrating total occlusion of the distal artery (arrow, left panel). After urokinase was infused for 8 h, angioplasty was successful, with a 10% residual stenosis (arrow, center panel). Six-month follow-up angiogram (right panel) demonstrates a patent vessel without restenosis.



angiographic complications. All patients who had unsuccessful angioplasty attempts had an uncomplicated hospital course without major complications.

There were no cases of abrupt vessel closure or recurrent in-hospital ischemia necessitating repeat intervention. Three patients (5%) exhibited elevated levels of creatine kinase, MB fraction after the procedure, but a level diagnostic of myocardial infarction (elevation >3 times normal) occurred in only one patient (1.6%). Four patients (7%) had bleeding complications requiring a blood transfusion; all of these complications were attributed to blood loss at the vascular access site. Transfusion requirements did not differ significantly among the groups (A 0%, B 15%, C 6%, $p = 0.14$). Gastrointestinal bleeding not requiring blood transfusion occurred in three patients (5%); two of the three had heme-positive stools and one patient had a Mallory-Weiss tear. Hematuria also occurred in two patients (3%). Combined bleeding complications including groin bleeding requiring blood transfusion, gastrointestinal bleeding and hematuria were more common in group B (25%) and group C (24%) than in the lowest dosing group A (4%) ($p < 0.05$ for group B or C vs. group A). Minor groin bleeding (hematomas) not requiring blood transfusion occurred more frequently in the higher dose groups (A 35%, B 43%, C 60%, $p = 0.2$), but differences were not statistically different.

Follow-up. Twenty-nine of the 32 patients with successful coronary angioplasty after the urokinase infusion underwent

functional stress testing at 3 months. Of these patients, 18 had no evidence of ischemia in the distribution of the target vessel, 4 had fixed defects and 7 had reversible perfusion abnormalities. Six-month angiograms were performed in 22 (69%) of the 32 patients. The remaining 10 patients refused angiographic follow-up but were asymptomatic and had negative results on functional tests. Target vessel patency, defined as a stenosis <100% and TIMI grade 3 flow, was maintained in 20 (91%) of the 22 patients with follow-up angiography. However, angiographic restenosis, defined as a residual diameter stenosis >50%, was seen in 13 (59%) of the 22.

Clinical 6-month follow-up on the 32 patients with procedural success was achieved in 97%. Symptom improvement was evaluated at 6 months by a practitioner who had no knowledge of coronary angioplasty results. A decrease in angina class or improved exercise tolerance was noted in 20 (63%) of the 32 patients with angioplasty success. There were no recurrent myocardial infarctions, strokes or deaths in the 6-month follow-up period. Clinical restenosis defined as the need for target vessel revascularization occurred in 13 patients (41%); elective bypass surgery was performed in 2 (6%) of these patients and repeat target vessel angioplasty in 11 (34%). The 6-month survival rate was 100%; of patients who underwent angiographic follow-up, 91% were alive with a patent target vessel and 60% were alive without the need for a repeat revascularization procedure. Of the 28 patients who had unsuccessful angioplasty after the urokinase infusions, only 4 (14%) noted a decrease in angina class or improved exercise tolerance. Follow-up data for all 60 patients who underwent attempted angioplasty after administration of urokinase demonstrated repeat percutaneous interventions in 11 (18%), bypass surgery in 9 (15%) and death in 0%. The majority (seven of nine) of the bypass operations were performed in patients who had unsuccessful angioplasty.

Table 2. Angioplasty Success After Urokinase Infusion

Vessel	Urokinase Infusion Group			Total
	A	B	C	
LAD	3/6	3/6	2/4	8/15
LCx	0/0	3/6	1/2	4/8
RCA	9/17	4/8	7/11	20/35
Total	12/23	10/20	10/17	32/60
Angioplasty success (%)	52%	50%	59%	53%

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery. See Methods for definitions of groups A, B and C.

Discussion

A prolonged infusion of urokinase has proved effective in the recanalization of chronic total occlusions in peripheral

arteries and saphenous vein bypass grafts (15,16). A pilot study (17) examining this approach for native coronary arteries demonstrated both safety and efficacy; however, the 24-h infusion utilized was costly and uncomfortable for the patient. Previous reports (18,19) have also documented the success of thrombolytic infusions for coronary angioplasty of chronic total occlusions. We were able to demonstrate that an 8-h infusion of intracoronary urokinase can frequently facilitate balloon angioplasty of chronic total occlusions >3 months old.

Rationale for recanalization of chronic total occlusions. Chronic total occlusions are the most frequent reason for angioplasty failure and referral for elective bypass surgery (5). Although many patients have had myocardial damage in the distribution of the occluded artery, collateral channels often maintain myocardial viability (20-22). If the total occlusion occurs in a highly diseased segment of the blood vessel without prior myocardial infarction, the collateral vessels also maintain viability, but the patient presents with a change in angina pattern (23). These collateral vessels usually supply sufficient blood flow to the affected area during times of physical inactivity but frequently become insufficient when oxygen demand is increased (20). Many patients therefore develop life style-limiting angina that is often refractory to maximized medications. Accordingly, attempts to treat chronic total occlusion with angioplasty are common and comprise 10% to 20% of all angioplasty procedures performed (24). The rationale for recanalization of chronic total occlusions includes the lessening of clinical symptoms (13), a decreased need for bypass surgery (9,13), possible improvement in left ventricular function (14,25) and improved survival (6). Decreased long-term survival is reported in patients with a chronic total occlusion of a single vessel treated medically (3,26), and a total occlusion has been associated with a higher incidence of sudden death than that of a high grade stenosis (27).

Mechanism. The composition of the chronic total occlusion has been shown to include a fibrocalcific atherosclerotic plaque and various degrees of organized thrombus (28). In contrast, fresh occlusions during myocardial infarction are composed of a ruptured fibrous cap overlying soft atheroma and a fresh, soft occlusive thrombus (29). In the chronic occlusion, layers of thrombi of different ages may be present, each of which is associated with fibrointimal proliferation (28). The age and the degree of fibrosis associated with the most recent thrombus is the single most important factor determining the likelihood of successful balloon recanalization (1,2,6,14,23,30,31). Attempts to pass a guide wire through these lesions often lead to recanalization of false lumens and resultant large dissections in the arterial wall. We had hoped to take advantage of urokinase's known ability to activate fibrin-bound plasminogen associated with thrombus, to lyse the thrombin component of the occlusion and restore anterograde flow in the native coronary artery. Although we did not observe dramatic improvements in flow after administration of urokinase alone, as assessed by TIMI grading, urokinase did appear

to soften the lesion, allowing passage of the guide wire. This effect is presumably due to partial lysis of the "freshest" thrombus occluding the lumen.

Success. Urokinase was able to facilitate angioplasty of chronic total occlusions in 55% of cases otherwise categorized as angioplasty failures. The urokinase infusion increased the angioplasty success rate for the 101 patients recruited from 41% to 72%, a rate that compares favorably with that of previous reports (1,2,11-13,32) on angioplasty of chronic total occlusions >3 months old. Because of the enrollment requirement of failed wire passage on initial attempts, all arteries underwent significant manipulation before urokinase administration. This factor probably led to an increased rate of vessel disruption and a higher dissection rate after angioplasty success was finally achieved. It is possible that starting the urokinase infusion before wiring attempts may increase acute procedural success and decrease long-term complications.

Follow-up success. The return of symptoms with a hemodynamically significant restenosis when the original occlusion was total is not unusual. This is secondary to derecruitment of collateral vessels after the initial successful angioplasty procedure (32). In contrast to results in previous studies (8,9) on chronic total occlusions, vessel patency was maintained in a high percentage (91%) of cases. All patients who did not undergo angiographic follow-up were asymptomatic with negative results on functional tests. Nevertheless, a high rate of angiographic restenosis was observed, which is consistent with previous studies (1,5,6,23,30). Given the high incidence of restenosis reported for these lesions, stent placement may be useful. Stents have been shown to reduce restenosis rates for elective angioplasty of native coronary arteries (33) and would probably also decrease long-term complications after angioplasty of chronic total occlusions.

Recommendations. Major complications including bleeding requiring transfusion were uncommon, making this approach to chronic total occlusions relatively safe. The two neurologic events (transient ischemic attack rate 3%) are of some concern; however, only one event occurred after initiation of urokinase. Patient immobility during the urokinase infusion is critical to minimizing bleeding complications, and adequate sedative and pain medications need to be administered to maximize patient comfort. Minor bleeding complications were more common in the higher dose groups, but success rates did not differ significantly among groups. Therefore, on the basis of our results, 50,000 U/h per port would be the dosage of urokinase recommended for this procedure. Because of the increased likelihood of vessel dissection after numerous wiring attempts, the urokinase infusion should probably be started before vigorous attempts to pass the guide wire beyond the occlusion. If recanalization is achieved, consideration should be given to stent placement in an attempt to lower reocclusion and restenosis rates.

Limitations of the study. Our study has four principal limitations. 1) By definition, all patients who were enrolled had unsuccessful coronary angioplasty. Therefore, within the de-

signed protocol, it was not possible to compare urokinase infusion with an infusion of placebo. Theoretically, the wiring attempts may have been more aggressive after the urokinase infusion or the heparin infusion may have been responsible for the increased success rates. This effect would have led to a falsely increased need for urokinase and cannot be ruled out because of the study design. Although our trial did involve randomization to different urokinase dosing regimens, there was no placebo infusion group. Because of this limitation, we cannot conclusively prove that the success after the infusion was solely the result of urokinase administration. However, before initiation of urokinase, all patients had failed attempts with an 0.018-in. standard wire which was considered failed angioplasty by current standards in our cath laboratory.

2) Angioplasty equipment has become more sophisticated since initiation of this study. The more common use of the 0.018-in. glide wire and laser-assisted guide wires may increase our ability to cross chronic total occlusions. Both of these new technologies, however, also increase the likelihood of finding false lumens possibly leading to an increased dissection or perforation rate, or both.

3) The sample size of 60 patients is relatively small, and further validation studies with larger patient groups are probably warranted. Nevertheless, urokinase was necessary for facilitation of angioplasty in 59% of cases, resulted in few bleeding complications, and it is currently recommended in light of this study's results, despite the fact that this study was observational without a placebo control group.

4) Although urokinase was the thrombolytic agent chosen for this study, other lytic agents including streptokinase or recombinant tissue-type plasminogen activator may have led to similar success rates. Testing of these other agents in comparison with urokinase will need to be done in future randomized studies.

Conclusions. An 8-h supraselective intracoronary infusion of urokinase offers the interventional cardiologist a treatment option in the recanalization of symptomatic total occlusions that have been unsuccessfully treated with prior angioplasty attempts with standard interventional techniques. Procedural success was achieved with lower dose regimens and was associated with less bleeding complications. Although vessel patency was frequently maintained, angiographic restenosis remains a problem. Nevertheless, the urokinase infusion significantly increased the overall rate of angioplasty success in chronic total occlusions >3 months old and lessened symptoms in a large majority of patients.

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